that the microsomal enzyme, steroid sulfatase, is deficient in all patients with recessive X-linked ichthyosis.

Diagnosis of this disorder may be established by several methods. Prenatally, it can be inferred from a characteristic profile of maternal estrogen excretion and confirmed through direct enzyme assay in cultured fetal amniocytes. Postnatally, steroid sulfatase activity can be assayed in cultured fibroblasts or fresh leukocytes. The diagnosis can also be inferred from the accumulation of cholesterol sulfate, a substrate of the enzyme, in scale from these patients and in serum and erythrocyte membranes. In serum, cholesterol sulfate is carried on predominantly low-density lipoproteins (LDL); in cases of recessive X-linked ichthyosis, accumulation of cholesterol sulfate in LDL results in increased electronegativity of these particles—hence their altered electrophoretic mobility on lipoprotein electrophoresis. Thus, a readily available standard laboratory test may be used for the diagnosis of this disorder.

Other forms of ichthyosis have also been linked to abnormalities in epidermal lipid metabolism. This association is not surprising in view of the structure of stratum corneum, in which anucleated, keratinized corneocytes are surrounded by an extracellular matrix composed of neutral lipids (especially alkanes, triglycerides, free fatty acids, cholesterol and ceramides). Alterations in the composition of the extracellular lipid matrix affect the normal process of desquamation. Cholesterol sulfate, a highly amphipathic lipid, is one of the few remaining polar lipids in stratum corneum. Its hydrolytic enzyme, steroid sulfatase, also localizes to the intercellular regions of stratum corneum. Continuing hydrolysis of cholesterol sulfate as corneocytes move outward may be a critical factor leading to normal desquamation. In the stratum corneum of patients with recessive X-linked ichthyosis, absence of steroid sulfatase activity results in continued high levels of cholesterol sulfate, reduced levels of free sterol and impaired desquamation.

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Subsets of Systemic Lupus Erythematosus

NEWLY DEFINED SUBSETS of lupus erythematosus are of value in defining prognosis and suggesting management approaches.

Subacute cutaneous lupus erythematosus is a cutaneous lupus variant characterized by mild systemic disease and slow therapeutic response. The lesions may be annular and polycyclic or papulosquamous and psoriasiform. Areas involved usually are the shoulders, upper chest and back. There is little scarring, photosensitivity is common and patients usually have mild systemic disease. Serologic markers of subacute cutaneous lupus include HLA-DR3 and the antibody anti-Ro (SSA [Sjögren's syndrome antibody]). In patients whose diagnosis is a problem, skin biopsy for hematoxylin-eosin stain and immunopathology should be done. In addition to the usual lupus serologic tests, studies for anti-Ro (SSA) antibody and HLA-DR3 may help to define the problem. It is important to differentiate the psoriasiform type from psoriasis, as therapy for psoriasis—that is, ultraviolet light—is contraindicated in patients with lupus.

Neonatal lupus erythematosus is a subset in which patients may or may not have cutaneous lesions. A "raccoon rash" is most common, though discoid and subacute cutaneous lupus lesions also occur. Mothers of these children may have clinical or serologic features of connective tissue disease. Systemic features of neonatal lupus include congenital heart block, hepatosplenomegaly and failure to thrive. Antinuclear antibodies are usually found, and the anti-Ro (SSA) antibody seems to be a marker in the patients and their mothers. The anti-Ro (SSA) antibody may be useful in prenatal screening of mothers with connective tissue disease and in identifying neonates at high risk for the development of congenital heart block.

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Leukotrienes—Their Importance in Dermatology

THE LEUKOTRIENES CONSTITUTE a group of derivatives of arachidonic acid that were so named because they were first isolated from preparations of leukocytes and were all found to possess three conjugated double bonds. Neutrophils, macrophages, eosinophils, basophils and some populations of mast cells are capable of generating leukotrienes. Leukotrienes C_4, D_4 and E_4 (abbreviated LTC_4, LTD_4 and LTE_4) are unique among the known metabolites of arachidonic acid—which include the prostaglandins and thromboxanes—in respectively having the tripeptide glutathione, the dipeptide cysteinyl-glycine and cysteine alone, linked to the arachidonic acid skeleton. LTC_4 and LTD_4 constitute the major part of the activity that was previously called slow-reacting substance of anaphylaxis. In the skin, these two compounds cause increased permeability of postcapillary venules. Most significant, LTC_4 and LTD_4 are at least 1,000-fold more potent on a molar basis than is histamine. When injected into human skin, LTC_4 and LTD_4 produce classic urticaria, suggesting that these agents may be involved in the production of some types of urticaria, especially those that are unresponsive to antihistamine therapy. Unlike the prostaglandins and thromboxanes, the generation of leukotrienes is not suppressed by most nonsteroidal anti-inflammatory drugs such as aspirin, indomethacin or ibuprofen. However, corticosteroids do inhibit the generation of leukotrienes as well as the prostaglandins and thromboxanes.

Another leukotriene, designated LTB_4, which does not

incorporate a peptide or any amino acid into its structure, is an extremely potent chemoattractant for neutrophils. When placed on human skin, LTB_4 will induce the influx of neutrophils into the epidermis and dermis. Of clinical interest is the observation that there are elevated levels of LTB_4 in the lesions of psoriasis that are characterized in part by their dense infiltrate of neutrophils. Because the neutrophil is a rich source of LTB_4, it is as yet unclear whether the elevated levels of this leukotriene in psoriatic skin are purely the result of the presence of the neutrophils or whether the skin is itself generating this chemoattractant. In this context, it should be mentioned that another arachidonic acid metabolite called 12-hydroxyeicosatetraenoic acid (12-HETE) is generated by isolated epidermal cells, is 80-fold to 100-fold elevated in psoriatic lesions and, like LTB_4, can cause the influx of neutrophils into human skin. Thus, this agent may be initially responsible for attracting neutrophils into the psoriatic skin, and these neutrophils, through their release of LTB_4, then attract more neutrophils. Such proposed pathogenic mechanisms have yet to be clearly established. However, both the presence and the biologic potency of the leukotrienes in human skin provide very strong justification for research that will address the possible roles in cutaneous disease of these relatively recently isolated lipid and peptidolipid mediators.

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Bovine Injectable Collagen

BOVINE INJECTABLE COLLAGEN (Zyderm Collagen Implant) has been approved by the Food and Drug Administration as a xenogeneic device available for soft tissue augmentation. It is used to correct small distensible cosmetic defects such as disease- or trauma-induced atrophy, postcosmetic surgical abnormalities, shallow acne scars and age-related wrinkles. It is not appropriate, for example, for correcting ice-pick scars or facial hemiatrophy.

The material is produced from bovine dermis that has been subjected to pepsin hydrolysis to cleave the more antigeneic telopeptides and make its implantation more immunologically acceptable to the human host. The resultant product is dispersed in saline solution containing 0.3% lidocaine and is available in two concentrations: 35% by volume of collagen (Zyderm I) and 65% by volume (Zyderm II).

Treatment with injectable collagen requires an initial screening skin test. Approximately 0.1 ml of the material is placed intradermally in the volar area of the forearm and the site evaluated over one month. A positive test consists of redness, swelling or both after six hours and contraindicates treatment. About 3% of persons will have a positive skin test. Nevertheless, despite one negative skin test, 1.3% to 6.2% of patients will have treatment-associated reactions of swelling and redness at the treatment site. These treatment reactions usually last four to six months and occasionally longer. To reduce the possibility of these reactions a second skin test a month after the first can be administered in a cosmetically inconspicuous area of the face and the treatment begun two to four weeks after a negative second test. Also, if a patient has not been tested or treated within a 12-month period, it is advisable to retest once to reduce the possibility of a treatment reaction.

Correction of defects requires two to three treatment sessions at two- to four-week intervals. At these visits the Zyderm collagen is implanted in the superficial papillary dermis by serial punctures of the skin with syringes prefilled with the material. In implanting the substance, one must deliberately overcorrect and observe a blanching of the skin with wheal formation at the injection site. Correction with collagen is temporary and requires periodic maintenance at 6- to 12-month intervals.

Treatment reactions to collagen are, for the most part, cosmetic and consist of redness and swelling at the treatment sites; mild systemic symptoms are, rarely, associated with these reactions. The only serious sequela is one case—out of more than 100,000 treated persons—of unilateral loss of vision due to probable inadvertent intraarteriolar injection. Treatment-associated reactions are almost uniformly associated with anti-Zyderm antibodies that do not cross-react with human collagen. Though patients with collagen vascular disease are excluded from therapy, the fear that injectable collagen would induce collagen disease has been shown to be unfounded in its eight years of use.

Presently, studies are underway utilizing bovine injectable collagen in other than cosmetic areas such as cases of esophageal reflux, laryngeal paralysis, bone grafting, urinary incontinence and corns and calluses. A more robust form of collagen that is longer lasting and of value in larger cosmetic defects is being evaluated.

To date, the considerable experience with injectable collagen attests to its safety and efficacy. Nevertheless, only future studies will define its ultimate role in the cosmetic and noncosmetic medical armamentarium.

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The Diabetic Hand Syndrome

SEVERAL RECENT OBSERVATIONS SUGGEST that a thickened dermis and limited joint mobility of the fingers may be a common finding in patients with diabetes mellitus. Painful, stiff hands were described as an uncommon complication of insulin-dependent diabetes mellitus as early as 1957. Subsequent descriptions of this syndrome in 1978 and 1980 showed that this phenomenon is a rather common finding in children with diabetes mellitus. About a third of children with diabetes have been noted to have limited joint mobility of the hands and